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Maria Ellis  
Executive Secretary for MEDCAC  
Centers for Medicare and Medicaid Services  
Center for Clinical Standards and Quality, Coverage and Analysis Group  
Room S3-02-01  
7500 Security Boulevard  
Baltimore, M.D. 21244

RE: Meeting of the Medicare Evidence Development and Coverage Advisory Committee—  
August 22, 2018

Dear Ms. Ellis:

Johnson & Johnson (“J&J”) is pleased to submit these comments regarding the upcoming meeting that will focus on the state of evidence on Chimeric Antigen Receptor (CAR) T-cell therapies that are approved by the Food and Drug Administration (FDA).

J&J is the world’s most comprehensive and broadly-based manufacturer of health care products for the consumer, pharmaceutical and medical devices and diagnostics markets. For nearly 130 years, we have supplied a broad range of products and have led the way in innovation, beginning with the first antiseptic bandages and sutures. We are continuing this heritage of innovation today, bringing important new pharmaceutical products to market in a range of therapeutic areas, as well as developing important advancements in medical devices and new consumer products.

This letter is submitted on behalf of the Janssen Pharmaceutical Companies (Janssen) of J&J. Janssen is dedicated to discovering and developing innovative medicines and solutions that transform individuals’ lives and, as an organization, we have expertise and experience measuring patient reported outcomes (PROs) in oncology clinical trials.

We are pleased to respond to the Centers for Medicare & Medicaid Services (CMS) request for advice, as part of the MEDCAC CAR T-Cell Therapy and PROs meeting announcement, on the appraisal of PRO instruments that can be used to generate evidence to inform patients’, caregivers’, providers’, regulators’, and payers’ decision-making as to the value of CAR T-cell therapies for the treatment of cancers among Medicare beneficiaries. This response addresses

the importance of PRO evidence to assess treatment value and offers our perspective on the Voting Questions for the panel convening in August, but does not comment on the necessity or appropriateness of a National Coverage Determination (NCD) for CAR T-cell therapies.

Janssen believes that:

- Understanding the patient perspective within our development programs is important and we support the collection of PROs
- PRO data need to be collected with rigor, using PRO instruments validated for the specific context of use and target population
- The demand for PRO evidence is high and continues to increase, though key stakeholders may have different needs and uses

Janssen and Legend Biotech have a CAR T-cell therapy program in early clinical development. While our thinking and measurement approach to capturing PROs continually evolves based on changing evidence needs of key stakeholders, current planned phase 2 clinical trials in this program include PRO endpoints. Our specific research objectives for including PROs in these early trials are two-fold: 1) to compare PROs after treatment to the individual's reported health state prior to CAR T-cell therapy; and 2) to assess the sustained benefit over time of the individual's perceived health-related quality of life (HRQoL) in response to treatment. We believe our measurement approach will generate robust, relevant, and timely evidence that will allow a clear evaluation of the patient perspective on our CAR T-cell therapy.

Earlier this year, the FDA approved apalutamide for the treatment of patients with nonmetastatic castration-resistant prostate cancer based on evidence from the SPARTAN trial (NCT01946204). A recent New England Journal of Medicine editorial by FDA officials spoke to the role PROs played in FDA's review and assessment of apalutamide's tolerability highlighting the importance of PRO evidence (Beaver J.A., Kluetz P.G., Pazdur R. (2018). Metastasis-free survival - a new endpoint in prostate cancer trials. *N Engl J Med*, 378, 26).

PRO endpoints of significant importance to measure as part of our CAR T-cell development program include disease-related symptoms, treatment tolerability and related impacts, physical function, and HRQoL. This approach aligns with the regulatory strategy to include PROs in single-arm trials of novel cancer drugs articulated by FDA officials during the agency's Third Clinical Outcome Assessments in Cancer Trials workshop on June 22 (PREVISIONPOLICY. (2018, July 2). Patient-reported outcomes in single-arm cancer drug trials among challenges discussed at FDA workshop. [www.previsionpolicy.com](http://www.previsionpolicy.com)). Our approach for developing a PRO strategy in oncology begins with understanding the disease, recognizing outcomes relevant to patients, and identifying what to measure followed by how best to measure these outcomes of importance. This also supports a key aspect of the National Quality Strategy: improving person- and family-centered care by ensuring that each person and family is engaged as partners in their care. Conducting foundational research demonstrating PRO instruments are fit for purpose in the population of interest is often necessary.

Given the importance of collecting PRO data with rigor and having PRO instruments validated for the specific context of use and target population, it will be beneficial for CMS to publicly

share how PRO evidence will be used to inform decision-making. Are proximal PRO concepts to a treatment's effect such as change in disease-related symptoms or tolerability considered of equal weight or are these of greater importance than more distal concepts such as cognitive, emotional, or social impacts and HRQoL? Knowing the PRO outcomes of interest to CMS and how the data will be used can better guide PRO instrument selection and timing of data collection in CAR T-cell development programs. As a first step, if not already undertaken, we encourage CMS to directly interact with Medicare beneficiaries to prioritize outcomes of importance. These outcomes may be different for various cancers, treatments, population age, and baseline health status.

It is not clear if CMS's interest is related to PRO evidence generated as part of a CAR T-cell registrational development program or for ongoing evaluation reflecting use in clinical practice. PRO instruments used for clinical research may not be fit for purpose in clinical practice and vice versa. Both types of PRO evidence could be of interest to CMS as well as other key stakeholders and each setting (i.e., clinical research and clinical practice) pose different opportunities and challenges to PRO evidence generation and communication.

Questions for CMS to consider include:

- How will PRO evidence be factored into decision-making?
- Will CMS consider PRO evidence outside of the FDA product label and published literature?
- Is there a plan to assess the validity of PRO instruments under consideration?
- Is there interest to capture PROs in clinical practice?

In response to Voting Questions for the panel convening in August, we offer our perspective to each below, but without more information and a better understanding of CMS's interest in PRO evidence on CAR-T therapies, our responses are qualified.

**1. How confident are you that each of the following PRO assessments are valid and generalizable to the Medicare population?**

*We are not confident that each of the PRO instruments are currently valid and generalizable since the Medicare population is heterogenous. Foundational evidence needs to demonstrate which PROs are of importance and that selected instruments used for measurement are fit for purpose in the Medicare population. All of the PRO instruments listed are validated for use in the adult population but limited evidence is currently available for the elderly and frail populations.*

**2. Considering all PRO assessments in question 1 with greater than or equal to score 2.5, please vote whether or not those PRO assessments combined have available supporting evidence on each of the following desired characteristics.**

*There are too many variables to summarize the evidence for the PRO instruments collectively. The context of use, application, ease of scoring and interpretation of results, and consideration of burden to the individual and healthcare system always need to be*

*considered when developing and implementing a PRO measurement strategy. The complexities associated with PRO data collection efforts and analysis are often unique to the severity of disease, the population, and the settings of care.*

## **Discussion Questions**

**Are there PRO assessments other than those listed in question 1 that have adequately stated evidence-based criteria and processes?**

*Yes, there are other PRO instruments validated for use in specific populations but without knowing the specific outcomes of interest CMS would like to measure, it is difficult to recommend alternatives for consideration. Knowing if there is interest to assess outcomes within a disease or across diseases guides PRO measurement strategy.*

**Are there additional desired characteristics other than those listed in question 2?**

- *Evidence generated from selected items or domains of legacy instruments may be more appropriate than total composite scores*
- *Defined meaningful change interpretation*
- *PRO instruments utilized in other CMS programs for oncology products*
- *PRO instruments appropriate for clinical trial programs, real-world evidence studies, clinical practice and electronic medical record collection*

**3. How confident are you that each of the following assessment intervals are appropriate measurement periods for a valid PRO assessment?**

- a. Variable event-dependent frequency interval (i.e. upon admission and after discharge)
- b. Fixed time-dependent frequency interval (i.e. weekly, monthly, or yearly)

*We are confident that each of the assessment intervals may be an appropriate measurement period but dependent on many factors largely driven by the outcomes of interest and when change may be expected. Sometimes a combination of the two (event-driven and time-dependent) may provide a more accurate and complete picture. Burden to the individual and healthcare system must always be considered.*

**4. How confident are you that a PRO assessment over the course of the following study durations identifies a meaningful durable treatment effect with a valid PRO?**

- a. 6 months
- b. 12 months
- c. 24 months

*We are confident that PRO assessment over different follow-up durations may be appropriate but dependent on many factors. Burden to the individual and healthcare system must always be considered. PRO evidence should always be evaluated in the context of treatment and along with important clinical endpoints such as disease progression and overall survival.*

**5. How confident are you that PRO assessments can provide meaningful results when studied with each of the following control populations?**

- a. patient him/herself, before and after intervention**
- b. usual care versus protocol-driven intervention**
- c. historical control**

*We are confident that each scenario has value and largely depends of the research question of interest, psychometric properties of the instrument, and how the evidence will be used to inform decision-making.*

Integrating the patient perspective in cancer drug development is of importance to many stakeholders who make decisions regarding the benefits and risks of cancer treatments and access to these life-saving therapies. Thank you for the opportunity to respond to this information request and Janssen looks forward to engaging with CMS on PRO measurement for CAR T-cell therapies in the Medicare population.

We appreciate the opportunity and the past collaborations with your staff to ensure the accuracy and fairness of Medicare's payments to hospitals. We look forward to continuing to work together on these and other issues.

Sincerely,

A handwritten signature in black ink, appearing to read 'Steve Phillips', with a stylized, cursive script.

Steve Phillips  
Senior Director, Global Health Policy  
Worldwide Government Affairs & Policy